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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
Before the United States International  
Preliminary Examining Authority  
for the Patent Cooperation Treaty

Applicants: Trustees of Dartmouth  
College et al.  
International Application No.: PCT/US99/25187  
International Filing Date: 28 October 1999  
Attorney Ref.: DC-0121

Honorable Commissioner of  
Patents and Trademarks  
Box PCT (IPEA/US)  
Washington, D.C. 20231

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By

  
Typed Name: Suzanne Spargman

Dear Sir:

Response to Written Opinion

This is in response to the Written Opinion mailed 16 March  
2001 setting a one-month period for reply.

**Rejection of Claims Under PCT Article 33(2)**

Claims 1-7 were suggested to lack novelty under PCT Article  
33(2) as being anticipated by Geyer et al. (1988). The Examiner  
suggests that this prior art reference teaches administration of  
methotrexate to adult rats via the lateral cerebral ventricle  
before irradiating the cervical spine, which resulted in  
protection against white matter necrosis and paralysis.

Applicants respectfully disagree with the Examiner's conclusions.

At the outset, only claims 1 and 2 claim use of methotrexate  
for treatment of pain. Claims 3-7 are unrelated to methotrexate  
specifically as they are drawn to an animal model for radicular  
pain and methods for producing an animal model of radicular pain.  
Nowhere in claims 3-7 is methotrexate claimed or suggested.

Therefore, this reference does not teach the limitations of the claims as filed and cannot anticipate claims 3-7 as suggested by the Examiner.

With regard to the rejection of claims 1 and 2 over Geyer et al. (1988), this paper discloses use of methotrexate in rats as a protective agent against the toxic effects of radiation, i.e., radionecrosis. Nowhere does this paper teach or suggest use of methotrexate as an analgesic agent for treatment of radicular pain. The teaching of protection against radiation damage is an entirely different pharmacological effect and is not related to analgesia. Accordingly, this reference does not teach the limitations of the claims as filed and cannot anticipate claims 1-2 as suggested by the Examiner.

**Rejection of Claims Under PCT Article 33(3)**

Claims 1-7 were suggested to lack an inventive step under PCT Article 33(3) as being obvious over Mori et al. (1996). The Examiner suggests that this abstract teaches administration of methotrexate to animals and demonstration of an analgesic effect in animals administered acetic acid to induce writhing. Applicants respectfully disagree with the Examiner's conclusions.

At the outset, only claims 1 and 2 claim use of methotrexate for treatment of pain. Claims 3-7 are unrelated to methotrexate specifically as they are drawn to an animal model for radicular pain and methods for producing an animal model of radicular pain. Nowhere in claims 3-7 is methotrexate claimed or suggested. Therefore, this reference does not teach the limitations of the claims as filed and cannot render obvious claims 3-7 as suggested by the Examiner.

Mori et al. (1996) is an abstract of a Japanese language paper that presents a review of the general pharmacological

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properties of methotrexate in animals. Although methotrexate was stated to show an analgesic effect in rats exhibiting an acetic acid-induced writhing syndrome (animals were administered oral doses of 3 mg methotrexate/kg or more), the abstract also states that the drug was without analgesic activity in another pain model, the mouse tail-flick response to thermal stimulation, even at oral doses as high as 30 mg/kg. Therefore, these data teach that methotrexate does not have analgesic activity in all models of pain. As a result, one of skill would not be able to predict (expectation of success) that the drug would be an analgesic in a model of radicular pain, as taught in the specification as filed. Additionally, the variable effects of methotrexate reported in this paper would not motivate one of skill to test the drug for analgesic activity in other models of pain. Accordingly, this paper does not render obvious the use of methotrexate to treat lower back pain with radiculopathy.

Respectfully submitted,

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Date: 02 April 2001

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